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14. ABSTRACT

There are two specific aims or categories of deliverables to be accomplished as tasks in this DoD sponsored research: The first specific aim is the hardware design and fabrication of a portable tactile diagnostic stimulator that can be used for the assessment of the cerebral cortical health of neurologically compromised subjects – in particular, those subjects with autism. The second specific aim is the development of tactile discriminative protocols that will be used for the evaluation of the differences in cerebral cortical function between subjects with and without autism. In this research project, all the milestones listed in the Statement of Work were met.

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Autism, functional Magnetic Resonance Imaging, Central Nervous System, Two Point Discriminative

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Introduction

There are two specific aims or categories of deliverables to be accomplished as tasks in this DoD sponsored research: The first specific aim is the hardware design and fabrication of a portable tactile diagnostic stimulator that can be used for the assessment of the cerebral cortical health of neurologically compromised subjects – in particular, those subjects with autism. The second specific aim is the development of tactile discriminative protocols that will be used for the evaluation of the differences in cerebral cortical function between subjects with and without autism. In the fourth year of research, all the milestones listed for Y04 in the Statement of Work were met, with some revisions or extensions of the original proposal. To summarize, we had originally proposed to continue to revise the two-point stimulator that we had developed. However, because our progress exceeded our original expectations in Y03, we advanced the prototype to the stage where we actually built a device which is not only more portable than originally proposed but has much more functionality. Our newest prototype is a 4 point ergonomically designed stimulator (fits any adult sized hand). This improvement in design allows for the new stimulator to address all questions previously addressed with two point stimulation as well as providing a platform to develop new protocols that utilize 4 fingers. The 4 point stimulator developed in Y03 was further modified in Y04 to be more ergonomic and a new prototype was also designed and fabricated that is magnet compatible. In other words, we have developed a 4 point stimulator that can be used in imaging systems (fMRI, MEG and MRS imaging). Additionally, both the two-point vertical displacement vibrotactile stimulator and the new prototype were used to assess and establish baseline values of the effects of conditioning stimuli on spatial and temporal integration in healthy subjects. Subjects with autism were also recruited and studied using the same protocols and the results from those studies show distinct differences in healthy and autistic subjects. The final milestone - to conduct studies to establish baseline measures of the impact of spatial and temporal integration – was also achieved. The methods that have been and are being developed via tactile sensory diagnostics allow for objective assessment of neurophysiological functional connectivity and could prove to be effective tools for noninvasive assessment of cerebral cortical function. In this final year Y05 of the project – which was an extension year – we continued to make refinements to the CM4 (the latest version of the 4 channel stimulator) in both hardware and software. Documentation of the CM4 was published (Holden et al, 2012) in Y05, and we made significant progress in refining analytical methods of the data that we collected.

Body

Milestone #1: *Design and fabrication of a portable diagnostic stimulator*

Contemporary methods for applying multi-site vibratory stimuli to the skin typically involve the use of two separate vibrotactile stimulators, which can lead to difficulty with positioning of stimuli and in ensuring that stimuli are delivered perfectly in phase at the same amplitude and frequency. Prior to Y01, we reported a two-point stimulator (TPS) that was developed in order to solve the problem of delivering two-point stimuli to the skin at variable distances between the sites of stimulation. Based on the original TPS, we designed and fabricated a new stimulator in Y01 with four significant improvements over our original device. First, the device is portable, lightweight and can be used in a variety of non-laboratory settings. Second, the device consists of two independently controlled stimulators which allow delivery of stimuli simultaneously to two distinct skin sites with different amplitude, frequency and/or phase. Third, the device automatically detects the skin surface and thus allows for much better automated control of stimulus delivery. Fourth, the device is designed for rapid manufacture and, therefore, can be made readily available to other research (non-laboratory) settings. An additional

significant revision of this device was made in Y02 that resulted in the device being more portable (this version is referred to as the CM-2). In this Y02 version, the DAQ interface was moved into the CM-2, and the only components that are necessary for subject testing are the CM-2 and a laptop. In Y03, we re-configured the device to fit into ergonomic housing and expanded the capability from 2-site to 4-site stimulation (model CM-4). In Y04, the system was made more ergonomic, software and hardware were further refined, and a new model was made (identical to the CM-4) that is magnet compatible and can be used in imaging studies.

Description of the Device

The Cortical Metrics (CM-1; see Figure 1) stimulator was developed in our laboratories for use in the series of experiments described in this report. The system was designed using state-of-the-art rapid manufacturing technology to allow multiple identical systems to be built and used in different locations. Also, the use of rapid manufacturing permitted very rapid design evolution, thereby potentiating the production of special fixtures and changes to geometry as needed for special applications, such as pediatric sizing or the use of special mounting hardware to adapt to existing equipment. The flat plates of the exterior housing and other components of approximately planar geometry are direct manufactured using laser-machined 6mm acrylic sheet, cut on a 120 Watt CO_2 laser engraving system, model number X660 (Universal Laser Systems, Scottsdale, AZ). The more complex housing and internal mechanism components are direct manufactured from polycarbonate (PC), by fusion deposition modeling (FDM) on a StrataSys Titan T-1 FDM (StrataSys, Inc., Eden Prairie, MN). All housing and mechanism components and assemblies were solid modeled prior to fabrication using SolidWorks solid modeling software (SolidWorks Corporation, Concord, MA).

Figure 1: First Version of Portable Tactile Diagnostic Stimulator

The electronics were designed using free CAD software from ExpressPCB (www.expresspcb.com). The printed circuit boards were manufactured using the resulting CAD files, also by ExpressPCB. The electronics employ 5 Microchip microcontrollers; four as dedicated motor controllers for the stepper motors and one as a central controller for the entire system. The hybrid circuit includes signal amplifiers for the position sensors, an analog controller to allow either “force” or “position” control of each VCA motor and tip, a tunable analog PID controller for position control of each tip, and a bipolar push-pull high-current op-amp output stage to drive each VCA motor. This configuration allows each VCA motor to be positioned and driven independently, while coordinated in terms of relative position (x-axis separation between the tips), tip-to-skin mechanical preload, tip vibration amplitude, frequency content, and phase.

The user interface is flexible, allowing several modes of operation. In the simplest mode, used for this series of experiments, a 40-pin ribbon cable connects the internal control logic and analog waveform circuitry directly to a National Instruments data acquisition system (NI DAQ USB-6251). Tip x and z positions, feedback adjustment, and tip vibration waveforms are generated by a laptop operating NI LabVIEW 7.1 which interfaces to the device using the parallel data cable via the NI DAQ system. In the second configuration, not used in this study, the stimulator system interfaces directly with the laptop via USB, and the intervening NI DAQ system and parallel cable are not needed. The first, simpler configuration was employed in this study because of the ease and convenience of developing tip stimulation waveform protocols using the NI DAQ analog output functions. In Y02, the external DAQ was replaced with an DAQ board internal to the CM-2.

In Y03, we initiated development of a 4 point stimulator device. To summarize, the above-described description of the device design of the two-point stimulator (CM-1) was reconfigured in housing that would allow for four-point stimulation. While the CM-1 device was still being utilized, a complete remodel of the device was initiated in order to make the system more portable and more ergonomic. The prototype of this device is pictured at the left. Note that in addition to being smaller, there are 4 sites of finger tip stimulation and the position of the stimulators is adjustable. Debugging of this device has been completed and we have begun using the device for data collection. In addition to improvements in ergonomics and portability, the device is much easier and more affordable to reproduce.

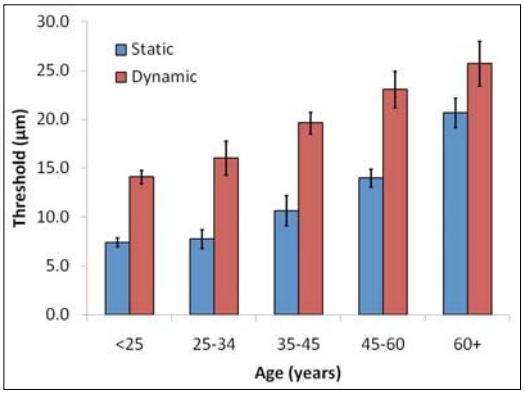
In Y04, we further improved the ergonomics of the device and began to re-design the configuration so that the entire system could fit into the forearm support. Note figure at left: ergonomics are improved by the change in shape of the forearm support. It is the forearm support pictured in the inset that will eventually house the entire system after we have completed re-design of the internal components of the main unit. The CM4 was documented via publication (Holden et al, 2012). Additionally, in Y05, we re-designed the internal components of the main unit and will be able to implement this new additional hardware in future revisions of the CM4. Our long term goal is to make this device as portable as possible so that it can be used in a number of clinical research environments.

Milestone #2: *Development of tactile discriminative protocols*

The CM-4 tactile stimulating device allows for simultaneous delivery of skin stimuli from four independently controlled stimulators that are mounted in a small, portable package that can be used on virtually any desktop. In our Y01 and Y02 report, we demonstrated that simultaneous amplitude discrimination tracking is a task that can be completed reliably and efficiently with the CM-1 and CM-2 systems, respectively. With the CM-4, we have achieved

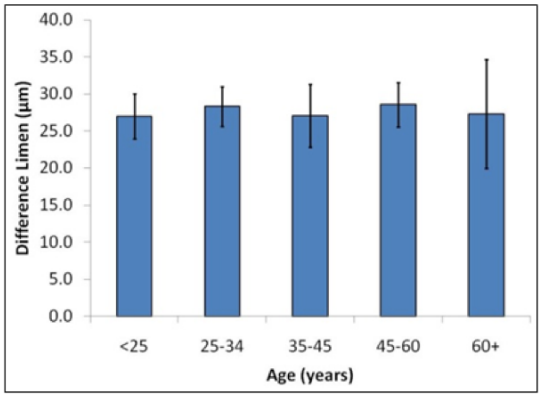
significant proof-of-concept that the all the protocols that the CM-1 and CM-2 were capable of can be delivered with the CM-4. Additionally, in Y04, we were able to demonstrate that the CM-4 is a reliable tool for assessing amplitude discriminative capacity of human subjects. One of our objectives in this work is determining what metrics are obtained can be reliable indicators of CNS health, regardless of age. Traditionally, sensory thresholds have been used as metrics for evaluating a number of conditions by clinicians, but they are very sensitive to age, and thus, cannot be reliable indicators for CNS health.

Our approach to threshold detection is slightly altered from the traditional approach. The majority of published studies report thresholds using one stimulus site, and subjects generally indicate whether they feel "something" or "nothing". Utilization of two stimulus sites allows for the subject to be questioned as to where they thought the stimulus was, and ultimately generates a more accurate answer.



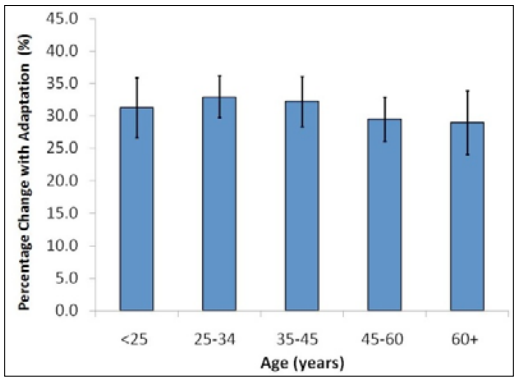
Our working hypothesis is that a centrally mediated measure will remain effectively constant across a subject population, provided that the CNS is healthy, although we would expect there to be a wide range in peripherally mediated measures. To demonstrate this concept, we examined thresholds across the healthy adult population. Due primarily to changes in skin physiology, detection thresholds go up (or sensitivity goes down) with age. Note in the graph at the right how threshold goes up with age. Also note that two types of threshold measures are shown – a "static" threshold in which a two-forced choiced paradigm is used to track threshold and a "dynamic" threshold in which a subject has to detect a modulated stimulus (increasing in size from zero to threshold level; also a two forced choice paradigm). The difference in the two results is currently postulated to be the result of feedforward inhibition at the level of layer IV in SI cortex, and thus, this metric that we have developed could be a very sensitive measure for detecting changes in the CNS.

In order to make the diagnostic tests more robust, we sought to improve the signal to noise ratio by increasing the stimulus size and having subjects make comparisons between two stimuli.

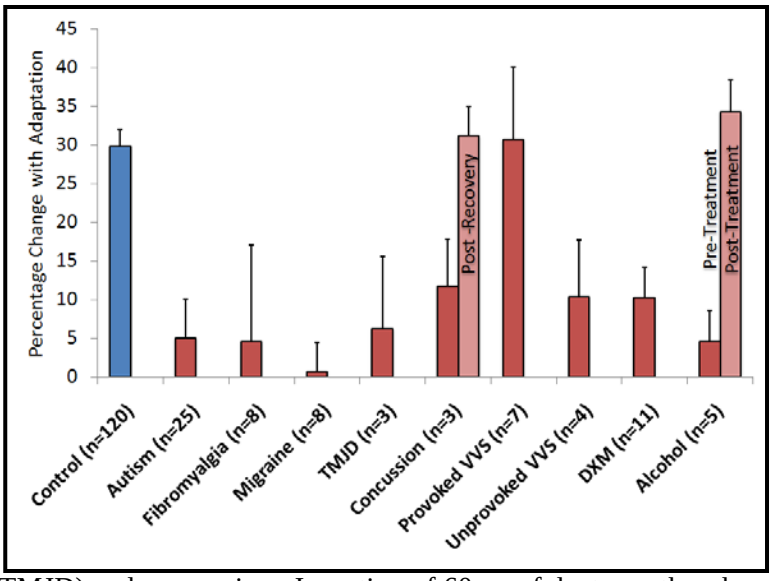


To test the idea that comparison of two adjacent stimuli is relatively stable in healthy populations, an amplitude discrimination task in which both stimuli were delivered simultaneously to adjacent finger tips (D2 and D3) was performed on healthy subjects across a wide age spectrum. This measure was effectively constant across all age groups (see Figure at left). It should be noted that, in order to maximize signal to noise ratio, we conduct this amplitude discrimination task at supra-threshold levels. This allows us to deliver the same size stimuli to all subjects and thus, although threshold variation (discounting for subjects with very significant peripheral neuropathy) is in the range of 10-30 microns, all subjects are able to effectively compare stimuli that are 100 microns or greater. The problem with amplitude discrimination as a potential clinical measure is that it is often *too* robust: Comparison of this measure between healthy controls and a number of subject populations demonstrated little significant difference. For this reason, we chose to examine more closely how different factors, and their underlying mechanisms, would impact amplitude discrimination capacity. Thus, we took advantage of the robustness of amplitude discriminative capacity at these stimulus

parameters in multiple subject populations by utilizing this measure as a baseline for each subject, and the critical measure for clinical purposes will be how this measure is altered under different experimental conditions.



Randomly applying a conditioning stimulus to one of the two skin sites before the amplitude discrimination task significantly alters a subject's ability to determine the actual difference between the two stimuli, and the impact that the conditioning stimulus has is duration dependent (between 0.2 and 2 secs; (for discussion, see Tannan et al., 2007a, 2008; Tommerdahl et al, 2007a, 2007b, 2008; Francisco et al, 2008; Zhang, et al, 2009).). This finding suggested that the method could be viewed as a reliable indicator of the influence of adapting stimuli on central nervous system response, as changes in the peripheral response are not significantly changed at these short stimulus durations. Simply stated, the reason that subjects get worse with conditioning stimulation to one of the stimulus sites is because the subsequent stimulus, which is used for comparison, now feels smaller than it really is. This creates an illusory effect which appears to be relatively constant across healthy populations regardless of age (see Figure at right). We published this data in Y05 (Zhang et al, 2012).

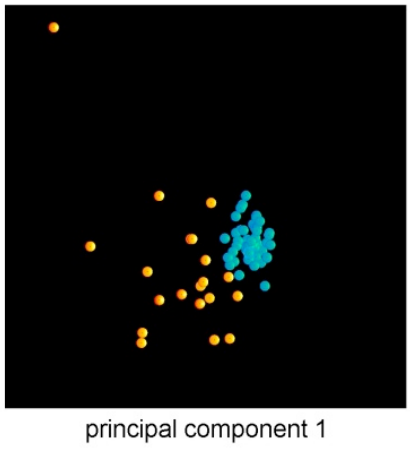


When this measure is examined across a number of subject populations (we initiated a number of pilot studies in Y04 by providing prototypes of the device to clinical researchers in a number of areas), we do see significant deviations from control values. To summarize, the chart below demonstrates that this centrally mediated measure deviates from the control values for subjects with autism (Tannan et al, 2008), chronic pain (fibromyalgia, migraine, TMJD) and concussion. Ingestion of 60mg of dextromethorphan (DXM) also leads to a reduction in the impact of the adapting stimulus (Folger et al, 2008) as does chronic use of alcohol. Values that appear in the control range are post-recovery of concussion (3-7 days after concussion) and post-treatment of alcoholism (12 weeks of sobriety; initial measure was after 1 day of sobriety and BAC was zero). "Provoked VVS" is considered peripherally mediated (and exhibits near control values) while "unprovoked VVS" is a chronic pain condition which is thought to be centrally mediated (Zhang et al, 2011). The significance of the VVS study is that distinct differences in information processing capacity (or central sensitization) of the two groups was detected by utilizing sensory testing methods on a body region (the finger tips) that was not impacted by the subjects' affliction (pelvic pain). In other words, pelvic pain had little or no

impact on subjects' thresholds, but it did have an impact on the subjects' centrally mediated neuroadaptation.

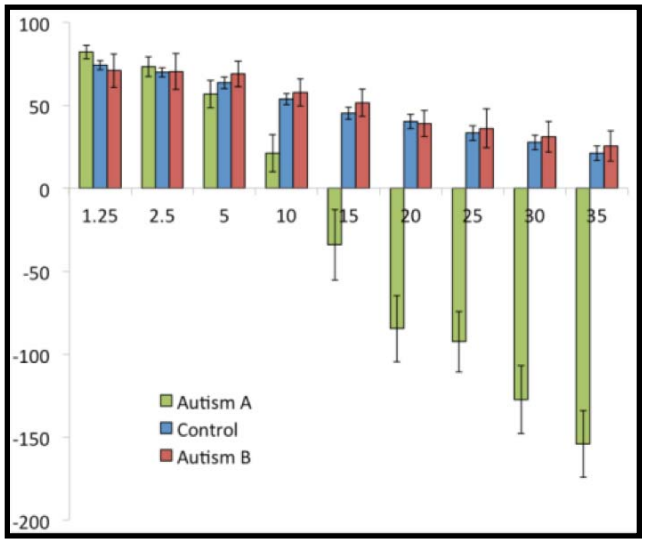
At first glance, the above-described method appears fairly non-specific: virtually all the data obtained from subjects with some type of centrally mediated neurological disorder is impacted. Adaptation, which encompasses the ability to quickly adjust to one's environment, involves a number of mechanisms. The protocols that have been designed to obtain neuroadaptation metrics were optimized to enable objective evaluation of the neuronal communication between adjacent and near-adjacent regions within sensory cortex that is widely recognized to be essential to normal sensory function. In other words, this "functional connectivity" between two adjacent or near-adjacent cortical regions is indicative of overall CNS functional connectivity. The mechanisms required for this communication include neurotransmission mediated by the inhibitory neurotransmitter GABA and by NMDA receptors, and interactions / interdependencies between neurons and glial cells. These particular processes have been demonstrated to have a significant impact on centrally mediated cortical adaptation, and thus, this type of diagnostic test could prove useful as a quick (2-3 minutes), reliable and efficient means for assessing CNS health. Diagnostic tests aimed at extracting more specific information about functional connectivity have been and will continue to be developed: This grant mechanism has provided an important catalyst to a new methodology which could prove to be useful in a number of clinical fields. Metrics obtained from multiple subject populations not only gives us information about the information processing capacities of those particular groups, but it gives us further insight into how the new metrics relate to the cortical information processing capacity of the autism population.

In Y05, we developed a new approach to assessing the differences between individuals with autism and typically developing individuals. A typical battery of protocols – such as the ones described above - lasts 20-30 minutes, and this yields multiple parameters that can be used to build a CNS profile of a subject. To fully appreciate the differences between subject populations, we utilized mathematical approaches for multi-variable analysis. Quantitative performance of each subject on the battery of *N* sensory tests is treated as localizing this subject in an *N*-dimensional "cortical metrics" space (i.e., an abstract space in which each coordinate axis corresponds to one of the battery's sensory tests). Principal Component Analysis (PCA) and Linear Discriminant Analysis (LDA; PLS-DA in particular) is used to graphically display the test-performance data collected in the different subject populations. The plot at the right, for example, was generated using PLS-DA on 8 metrics, and it clearly separates individuals with autism (orange) from TD controls (blue) with a 99% confidence level that the two populations are different (using t-squared Hotelling test). Our aim, in future studies currently being proposed, is to determine if treatments will result in a shift towards control values.

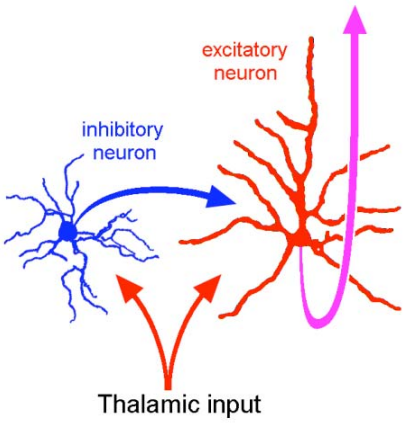


One of the major issues in autism being studied today is its heterogeneity. That is, not all people with autism have autism because of the same genetic and environmental impacts, and in Y05 we investigated potential differences in information processing capacity within the spectrum. Understanding the differences in the way the brain processes information within this subject

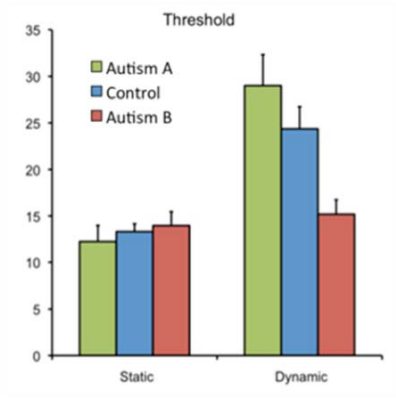
population may prove to be essential for determining what treatment, whether it be behavioral or pharmacological, should be administered. Several tests to measure the temporal integrative capacity of subjects were developed. Comparisons of results between healthy subjects and subjects with autism continues to suggest that the cortical circuitry of individuals with autism is functionally distinctly different from that of healthy adults. In particular, we have developed new protocols which show that some autistics are sensitive to different modulation rates of stimulation while others are not. As heterogeneity of the autism spectrum is an important problem to address, we will pursue this line of research. One of the principle findings of heterogeneity that is beginning to emerge from our data set is that results from autism subjects cluster into one of two groups, with one of the groups being much more deviant from the data obtained from healthy controls than the other. Counter-intuitively, this group typically scores closer to normal on the ADOS. These findings will continue to be investigated, but it is beginning to clearly appear that our methods are able to describe the heterogeneity of the autism spectrum in a quantitative manner. The autism spectrum appears to be clearly divided based on rate dependent cortical information processing capacity. In the figure at the above left, we compared the matching capacity of subjects with autism with controls. One stimulus was held at a stationary value, while another stimulus was increased from zero up to an intensity that the subject indicated the percept was equal to the larger stimulus. At low rates of stimulus amplitude increase (see graph at left), all subjects perform about the same. However, at the higher rates of stimulus intensity increase, there is a divergence in performance, and the autism population split into one group that performed in a manner similar to controls and another that was very different.



A major well-documented feature of cortical functional organization is the presence of prominent feed-forward inhibition in the input layer 4 (see figure at right), in which local layer 4 inhibitory cells receive direct thalamocortical input and in turn suppress responses of neighboring layer 4 excitatory cells to their thalamocortical drive, thereby sharpening their RF properties (e.g., Douglas et al. 1995; Miller et al. 2001; Bruno and Simons 2002; Alonso and Swadlow 2005; Sun et al. 2006; Cruikshank et al. 2007). These inhibitory cells are more responsive to weak (near-threshold) afferent drive than are the excitatory layer 4 cells and thus they ***raise*** the threshold at which excitatory layer 4 cells begin to respond to peripheral stimuli.



Sensory testing of stimulus detection threshold is particularly well-suited for probing the impact of sub-threshold conditioning or feed-forward inhibition, considering that stimuli just below the detection threshold will be too weak to engage other layer 4 mechanisms besides thalamocortical excitation and feed-forward inhibition (such as lateral excitation, recurrent or feedback inhibition, or activity-driven adaptation).



In our comparative study of typically developing vs. autism individuals, we found that subjects with autism exhibit significantly greater diversity in their detection thresholds on fingertips than control subjects, with two groups emerging (designated as Group A and Group B). Based on cluster analysis of several measures, the data that we have obtained thus far strongly suggests two distinct clusters within the spectrum. Group B autism individuals have dynamic thresholds lower than controls (thus suggesting reduced feed-forward inhibition) and group A autism individuals have dynamic thresholds higher than controls (thus suggesting enhanced feed-forward inhibition). Inhibitory neurogliaform cells in layer 4 use both $GABA_A$ and $GABA_B$ receptor-mediated inhibitory synaptic transmission (Tamas et al. 2003; in other inhibitory cell classes $GABA_B$ receptors are located in the presynaptic membrane and used for autocontrol). $GABA_B$-mediated inhibition develops and lasts much longer than $GABA_A$-mediated inhibition. We believe we detect the $GABA_B$ component of feed-forward inhibition in our new, "dynamic" variant of the basic ("static") detection threshold test, in which we deliver vibrotactile stimuli of gradually increasing amplitude (starting at zero and growing at a rate of 2 microns/sec) until the subject detects the vibration. Interestingly, this time-extended mode of stimulus delivery prominently elevates the detection threshold (compare "static" and "dynamic" plots in the figure at above left), presumably by fully activating slow $GABA_B$ inhibition in addition to fast $GABA_A$ inhibition. Again we find that autism subjects exhibit greater diversity on this test than controls: group A autism individuals have static thresholds below controls, but dynamic thresholds above controls (suggesting reduced $GABA_A$ inhibition, but elevated $GABA_B$ inhibition), while group B autism have the opposite relations. The significance of this finding is that if alteration of GABAa vs. GABAb inhibition influences the impact of subthreshold mediated activation, then it implies that the 2 aforementioned autism populations should, if treated pharmacologically, would respond differently to a GABAb agonist, such as baclofen. If this is the case, then a simple metric could potentially predict whether or not this particular treatment would be effective.

Key Research Accomplishments

- Evolution of a portable two-point stimulator to a four-point stimulator
- Development of novel protocols of cortical information processing assessment
- Collection of baseline data from healthy subjects for spatial and temporal integration tasks
- Collection of baseline data from autism subjects for spatial and temporal integration tasks
- Demonstration that a number of baseline metrics are reliable across the age spectrum
- Demonstration that sensory information processing profiles of individuals with autism is distinctly different from typically developing individuals with a 99% confidence level
- Publication/documentation of CM4
- Publication of baseline control metrics for a wide age spectrum

Reportable Outcomes

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Personnel receiving pay from this research effort:

Mark Tommerdahl
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Conclusion:

The development of unique quantitative sensory testing methods was made possible by the design and fabrication of a portable two-point vibrotactile stimulator (and recently, subsequent design and fabrication of a portable four-point vibrotactile stimulator). The sensory testing methods and apparatus that were developed were designed to enable objective evaluation of the elaborate neuroanatomical connectivity that sub serves the neuronal communication between adjacent and near-adjacent regions within sensory cortex that is widely recognized to be essential to normal sensory function. There have been several significant findings in the early stages of applications of these methods in our autism research. First, results comparing the spatial localization ability of subjects with autism vs. controls demonstrated that although cutaneous localization performance

of adults with autism is significantly better than the performance of control subjects, tactile spatial discriminative capacity remained unaltered in the same autism subjects when examined after the duration of adapting stimulation was increased although significant improvement was observed in controls. Second, results comparing the ability of subjects with autism to discriminate between the intensity of two simultaneously delivered stimuli demonstrated that although autism subjects were equal to or better than control subjects at short duration discrimination tasks, conditioning stimuli delivered prior to a task had no impact on the autism subjects' ability to discriminate although this conditioning had significant impact on control subjects' perception. Both the failure of prior history of tactile stimulation to alter sensory percepts in adults with autism, and the better-than-normal perceptual performance of adults with autism in these tasks, were concluded, in the above-mentioned studies, to be attributable to both the smaller than normal minicolumn width observed in autism subjects and the deficient cerebral cortical GABAergic inhibitory neurotransmission characteristic of this disorder. A third study examined the effective short-range functional connectivity of subjects with autism vs. neurotypical controls, and significant differences were found between controls and autism subjects in the influence that synchronizing stimuli have on sensory perception. An important emerging concept in autism research is the role of dysfunctional neural synchrony, and it was speculated from these recent findings that the local functional connectivity that normally sub serves long range connectivity and synchrony could be a result of the abnormal minicolumn architecture that has been previously reported by others. One unifying theme of these findings is the role that cortical modularity plays in sensory information processing, and in autism, cortical modularity is disrupted to an extent that significant quantifiable deficits in sensory information processing can be detected. In terms of practical application, future work could mean that the methods that we are developing could be used for both basic diagnostic applications as well as determination of efficacy of intervention. New research studies are currently being proposed by multiple teams of investigators that will utilize the technology that we developed as a result of this grant, and some of those studies will be evaluating the potential of the method for predicting treatment outcomes: based on our observation of distinct heterogeneity within the autism population, different treatments could be more effective for subsets of the autism population. It should also be noted that the utility of these methods is not limited to their application to the field of autism. The methodology that was developed under this grant mechanism has enormous potential to provide a number of clinical fields with low cost, high throughput, biologically based, efficient and effective diagnostic tools.

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Appendices:

The following papers are included in the Appendix:

Holden JK, Nguyen RH, Francisco EM, Zhang Z, Dennis RG and Tommerdahl M (2012) A novel device for the study of somatosensory information processing. J Neurosci Methods, Mar 15;204(2):215-20. Epub 2011 Dec 4.

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Basic Neuroscience

A novel device for the study of somatosensory information processing

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ABSTRACT

Current methods for applying multi-site vibratory stimuli to the skin typically involve the use of multiple, individual vibrotactile stimulators. Limitations of such an arrangement include difficulty with both positioning the stimuli as well as ensuring that stimuli are delivered in a synchronized and deliberate manner. Previously, we reported a two-site tactile stimulator that was developed in order to solve these problems (Tannan et al., 2007a). Due to both the success of that novel stimulator and the limitations that were inherent in that device, we designed and fabricated a four-site stimulator that provides a number of advantages over the previous version. First, the device can stimulate four independent skin sites and is primarily designed for stimulating the digit tips. Second, the positioning of the probe tips has been re-designed to provide better ergonomic hand placement. Third, the device is much more portable than the previously reported stimulator. Fourth, the stimulator head has a much smaller footprint on the table or surface where it resides. To demonstrate the capacity of the device for delivering tactile stimulation at four independent sites, a finger agnosia protocol, in the presence and absence of conditioning stimuli, was conducted on seventeen healthy control subjects. The study demonstrated that with increasing amplitudes of vibrotactile conditioning stimuli concurrent with the agnosia test, inaccuracies of digit identification increased, particularly at digits D3 and D4. The results are consistent with prior studies that implicated synchronization of adjacent and near-adjacent cortical ensembles with conditioning stimuli in impacting TOJ performance (Tommerdahl et al., 2007a,b).

1. Introduction

For the past several years, our research group has been working towards the development of a portable tactile stimulator that could effectively be used to study changes in sensory information processing in clinical and clinical research venues across a diverse spectrum of neurological disorders. Thus far, we have gone through several iterations in the development of this stimulator. The first prototype of the device (Tannan et al., 2005a) was used to demonstrate changes in spatial acuity with repetitive stimulation. A subsequent report described that this change did not occur with individuals with autism, strongly suggesting a lower-than-normal inhibitory response (Tommerdahl et al., 2007a). A second iteration of the device (Tannan et al., 2007a) was much more portable as well as more robust and reliable in its ability to deliver well-controlled vibrotactile stimuli to the skin. The device proved extremely useful, and a number of studies were conducted with it that demonstrated the ability to reliably and reproducibly obtain metrics of neuro-adaptation (Tannan et al., 2007b), temporal order judgment (TOJ) and the impact of synchronized conditioning stimuli on TOJ (Tommerdahl et al., 2007b), the absence of the impact of those same conditioning stimuli on TOJ in individuals with autism (Tommerdahl et al., 2008), the relationship between spatial acuity and amplitude discrimination (Zhang et al., 2008), a method for the study of tactile-thermal interactions (Zhang et al., 2009), a reliable means for measuring amplitude discriminative capacity and a robust near-linear relationship between duration of repetitive conditioning stimuli and the impact of that conditioning on amplitude discriminative capacity (Tannan et al., 2007b), the below-normal adaptation metrics in autism (Tommerdahl et al., 2007a,b), the impact of NMDA receptor block on adaption metrics (Folger et al., 2008), a demonstration of Weber's law (Francisco et al., 2008; Holden et al., 2011) and a robust relationship with neurophysiological data (Francisco et al., 2008), and differences in timing perception in Parkinson's Disease (Nelson et al., 2011). More recently, we have developed a newer, more portable and ergonomic model of the device, which is much more suited for a clinical or clinical research environment, and is capable of delivering vibrotactile stimuli to four fingers: the index (D2), middle (D3), ring (D4),

Abbreviations: TOJ, temporal order judgment; NMDA, N-methyl-D-aspartate; FDM, fusion deposition modeling; VCA, voice coil actuator; CAD, computer-aided design; AFC, alternative-forced choice; DL, difference limen.

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and little (D5) fingers. The utility of this device has been recently reported in a paper that reported phenotypic differences within a spectrum of patients with vulvodynia (Zhang et al., 2011), and in a paper that describes its utility for describing phenotypic differences within the autism spectrum via modulating vibrotactile stimuli (i.e., sinusoidal stimuli that dynamically change in amplitude), but the device itself, as well as a demonstration of its capability to deliver four-digit protocols, has not been fully described, which is the purpose of this report. In a subsequent paper, a magnet-compatible version of this device will be reported.

2. Methods

2.1. Hardware

The cortical metrics (CM-4; see Fig. 1) stimulator was developed in our laboratories for use in series of experiments such as those described in this report. The system was designed using state-of-the-art rapid manufacturing technology to allow multiple identical systems to be built and used in different locations. Also, the use of rapid manufacturing permitted very rapid design evolution, thereby potentiating the production of special fixtures and changes to geometry as needed for special applications. The device consists of two separate parts: the main body and a detachable head unit. The flat plates of all exterior housing and other components of approximately planar geometry are direct manufactured using laser-machined 6 mm acrylic sheet, cut on a 120 W CO_2 laser engraving system, model number X660 (Universal Laser Systems, Scottsdale, AZ). The more complex housing and internal mechanism components are direct manufactured from ABS plus, by fusion deposition modeling (FDM) on a StrataSys Dimension bst 1200es (StrataSys, Inc., Eden Prairie, MN). The cylindrical trays forming the disks of the head unit are CNC machined from 1 inch thick Acetal (Delrin) plate. All housing and mechanism components and assemblies were solid modeled prior to fabrication using SolidWorks solid modeling software (SolidWorks Corporation, Concord, MA).

The internal mechanism of the head unit is comprised of identical cylindrical disks placed sideways and four abreast (130 mm in diameter, 11 mm in depth) between two plastic supports. Each disk can be independently rotated to adjust for differing finger lengths for each test subject. A voice coil actuator (VCA) and an optical position sensor are mounted in each disk. Each VCA is attached to a plastic probe (5 mm diameter), which slightly protrudes through a hole (7 mm diameter) in the side of the cylinder. The amount of protrusion for each probe is independently adjustable as are the positions of the holes to accommodate the length of the subject's fingers. The VCAs drive the plastic stimulator probe tips according to prescribed sinusoidal waveforms. The moving components of the stimulator tips are directly manufactured from polycarbonate (PC) by 3-D FDM as a single compliant mechanism component integrating a mounting flange, a thin-beam four-bar linkage, a magnet coil bobbin, an optical displacement sensor vane, and the extension to the mechanical stimulator tip. The compliant four-bar linkage mechanism allows the coil, optical position sensor vane, and tip to be displaced vertically along a straight line for a distance of ± 1 mm. The 4-bar compliant mechanism also provides a very low hysteresis linear restoring force to center each tip vertically when no current is applied to the VCA coil. The VCA coil is 400 turns of 34 AWG magnet wire (approximately 30 Ω total resistance), wrapped in a rectangular bobbin permanently solvent bonded into the four-bar mechanism. The entire four-bar mechanism is 5.3 mm in thickness, and is positioned such that the VCA coils sit directly between two opposed rectangular N42 rare-earth-element magnets (catalog number BCC2, K&J Magnetics, Jamison, PA) similar to those found in computer hard drives. The resulting VCA motors generate extremely linear force outputs as a function of drive current with very low hysteresis due to the "frictionless" nature of the single-piece bearing-less four-bar compliant mechanism. The position of the vibrating tips is detected by non-contacting optical displacement sensors, one for each tip, similar in configuration to ones we have previously employed in precision optical force transducers (Dennis and Kosnik, 2002). When the tips are not being driven, the optical position sensors can act as a highly sensitive contact or force sensor. By employing the optical position sensor, the tips can be driven to contact the skin, and the contact force of each tip can be adjusted independently due to the fact that the spring constant of each VCA four-bar linkage mechanism is identical.

The custom electronics were designed using free CAD software from ExpressPCB (www.expresspcb.com). The printed circuit boards were manufactured using the resulting CAD files, also by ExpressPCB. The hybrid circuit includes signal amplifiers for the position sensors, an analog controller to allow either "force" or "position" control of each VCA motor and tip, a tunable analog PID controller for position control of each tip, and a bipolar push–pull high-current op-amp output stage to drive each VCA motor. This hybrid circuit is interfaced via four parallel pin connectors (2 banks of 50 pins for digital signals and 2 banks of 34 pins for analog signals) to an internal NI-USB-6259 data acquisition (DAQ) board. The DAQ board then interfaces via a USB connection to any standard PC running Microsoft Windows XP or later.

Fig. 1. Four site vibrotactile stimulator. Each of the four probe tips is positioned by rotating the four independently positioned drums to maximize contact between finger pads and the stimulator tips. During an experimental session, subjects were seated comfortably in a chair with their arm resting on the arm rest attached to the head unit of the device. Digits D2 through D5 were then positioned for vibrotactile stimulation.

2.2. Software

A custom line-of-business application was developed for the Microsoft. Net platform using the C# programming language and Windows Presentation Foundation (WPF) framework to control the stimulator and to administer the data collection protocols. The interface was designed to be intuitive, extensible, and aesthetically pleasing. The software needed to be extensible to facilitate the development of future protocols for a device as flexible as the CM-4. The core extensibility was achieved by using a "plugin" architecture with a shell application whose function is to discover, load and execute small plugins. The shell exposes a software contract (an inheritable C# class) that is consumed and extended by each plugin. Each task described in this paper represents one such plugin. Most traditional neuropsychological protocols using the standard X-alternative forced-choice (X-AFC) tracking method (Cornsweet, 1962) can be created with only a couple dozen lines of C# code. While most plugins interact directly with the CM-4 stimulator, this is not a requirement of the plugin contract. Plugins can, for example, be designed to collect arbitrary subject information pertinent

to the given study (e.g. participant demographics, relevant medical history, various surveys, etc.). The net effect is not only a significant reduction in the amount of clinical paperwork that needs to be completed by each participant, but also a marked reduction in data-entry time for clinicians. All data collected by the application are stored in an encrypted (128-bit RC4) SQLite database in a user-specified location. Each database can be shared with multiple instances of the shell application, providing a mechanism for seamless networking of CM-4 stations (Holden et al., 2011). The software is also capable of storing, as well as creating and customizing, all relevant initialization information for each plugin, such that a given battery of protocols can be administered repeatedly and in a consistent manner, while maintaining flexibility for future projects. The batteries allow for greater reuse of each plugin, resulting in shorter development times a more efficient workflow throughout an experiment.

2.3. Protocols

In order to demonstrate exemplary use of the CM-4, a finger agnosia test, in the presence and absence of conditioning stimuli, was performed. The finger agnosia test was designed to assess the capacity of subjects to recognize and identify stimulated digits, an assessment similar to tactile finger recognition or localization tests (Boll, 1974; Reitan and Wolfson, 1993) utilized in current neuropsychological diagnostics.

2.4. Subjects

Seventeen healthy subjects (8 males and 9 females), ranging from 22 to 57 (39.1 ± 2.9) years of age, were recruited for the study. None of the subjects reported any neuropsychological impairment and all were naïve to both the study design and issue under investigation. The study was performed in accordance with the Declaration of Helsinki, all subjects gave their informed consent, and the experimental procedures were reviewed and approved in advance by an institutional review board.

2.5. Experimental procedure

During an experimental session, the subjects were seated comfortably in a chair with the right arm resting on the device. Because the lengths of fingers typically vary among subjects, the positions of the probe tips were individually adjusted to ensure that they contacted the glabrous, padded tips of the fingers of each subject. These loci were chosen in order to allow the convenience of access and comfort of participants as well as for the wealth of neurophysiologic information that exists for the corresponding somatotopic regions of cortex in primates (Chen et al., 2003, 2007, 2009; Francisco et al., 2008; Friedman et al., 2008; LaMotte and Mountcastle, 1975; Mountcastle et al., 1969; Tommerdahl et al., 1993, 1998, 2002, 2005, 2006, 2010). As depicted in Fig. 1, probe tip positioning was accomplished by loosening a set screw and rotating each of the drums independently to conform to the natural hand shape of each subject. After proper positioning, if the probe tips still failed to make proper contact with the digits, the tips themselves were either raised or lowered. Once adjusted, the probe tips were locked in place prior to initiation of the battery so that they would remain immobile during testing. At the start of each run, the four tips were driven towards the tips of the fingers in order to ensure good contact with the skin.

During the assessment, the device delivered constant-amplitude sinusoidal skin displacements (vibrations) via flat Delrin probes (5–10 mm in diameter) positioned to make contact with the tips of the index (D2), middle (D3), ring (D4), and little (D5) fingers of the right hand. The independent probe tips were computer-controlled and capable of delivering a wide range of vibrotactile stimulation of varying frequencies (Hz) and amplitudes (μm). Stimulus parameters were specified by test algorithms that were based on specific protocols as well as subject responses during those protocols.

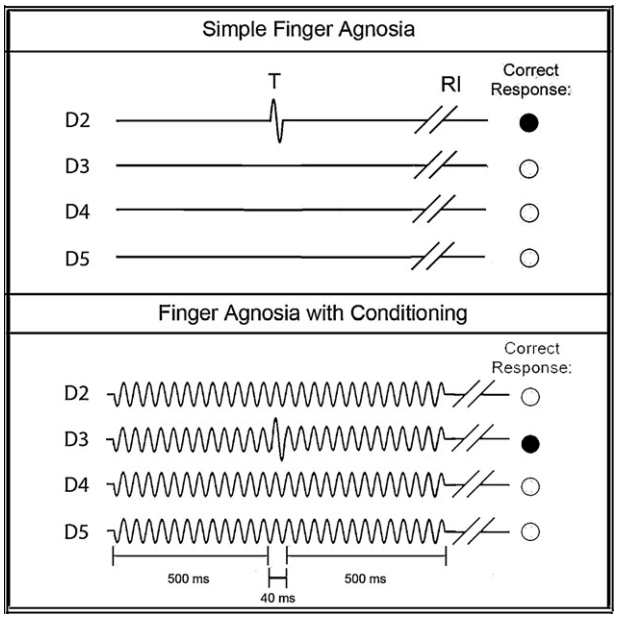

Fig. 2. Schematics of finger agnosia protocols. The simple finger agnosia assessment (top panel) consisted of a 4AFC protocol where a short test (T) pulse (300 μm, 25 Hz, 40 ms) was delivered to one of the four digits followed by a subject response interval (RI). The finger agnosia test was also conducted in the presence of conditioning stimuli of amplitudes 30, 40, 50, or 100 μm (bottom panel). The conditioning stimulus was delivered 500 ms prior to, and 500 ms following, the tap of the test digit. For all finger agnosia tasks, subjects indicated which finger was perceived to have received the large amplitude tap by choosing the respective digit on an image of the dorsal side of a hand presented on a computer monitor. Test stimuli sites were pseudo-randomized on a trial-by-trial basis.

Subjects viewed a computer monitor that provided continuous visual cueing during the experimental session. Specifically, an onscreen light panel indicated to the participant when stimuli were being delivered and when subjects were to respond. Training trials were not included prior to testing, and the subjects were not given performance feedback or knowledge of the results during data acquisition. The sensory testing session was conducted by application of low frequency (25 Hz) vibration to selected fingers. Each battery of testing lasted between 15 and 20 min depending on the protocols being run and on subject performance. Each individual protocol typically lasted 2–3 min.

2.6. Finger agnosia protocol

Finger agnosia tests are typically utilized to diagnose the ability of subjects to recognize and identify stimulated digits (Boll, 1974; Reitan and Wolfson, 1993). In order to assess the ability of the subject to discriminate one digit from another, a four-alternative forced-choice (4-AFC) protocol was implemented. Fig. 2 represents a timeline for the finger agnosia protocols evaluated. The device delivered a short pulse or tap (300 μm, 25 Hz, 40 ms) to one of the four digits in a pseudo-random order on a trial-by-trial basis, and subjects were queried as to which digit was stimulated (Fig. 2). The simple test was used in order to determine baseline values for each subject. A more complex agnosia test was subsequently administered in which test stimuli were delivered to the skin as a tap as in the previous test (300 μm, 25 Hz, 40 ms), but in the presence of conditioning stimuli at variable amplitudes. In each case, a 25 Hz, 500 ms conditioning stimulus was delivered to all four digits

at one of four amplitudes: 30, 40, 50, and 100 μm. The conditioning stimulus was delivered 500 ms prior to, and 500 ms following, the tap of the test digit (Fig. 2). For all finger agnosia tasks, subjects indicated which finger was perceived to have received the large amplitude tap by choosing the respective digit on an image of the dorsal side of a hand presented on a computer monitor. Test stimuli sites were pseudo-randomized on a trial-by-trial basis. The subjects were assessed on their accuracy over a total of 16 trials (4 trials for each digit as the test stimulus).

2.7. Analysis

For the finger agnosia protocols, accuracy percentages were calculated by analyzing the ratio of correct to total responses of the subjects. Percent accuracies were trial-independent and reflected accuracies across all 16 trials. The 100 μm conditioning condition was chosen for further analysis because of the significantly lower percent accuracy compared to the simple agnosia task. Percent inaccuracies were quantified for the 100 μm conditioning stimulus by calculating the frequency at which digits were incorrectly chosen. Results were calculated in this manner in order to compare percent inaccuracies with difference limens (DLs), where lower value might suggest higher accuracies and increased discriminative capabilities. The data were analyzed for significance by calculating p-values across mean inaccuracy metrics for each digit. Histograms were plotted in order to visualize the differences among each of the digits with respect to standard error of the means. Statistical t-tests were used to evaluate the difference of the performance of each subject under different conditions. A probability value of less than 0.05 was considered statistically significant.

2.8. Auditory cue analysis

To ensure that the stimulator did not produce any audible cues during the agnosia task, an auditory output analysis was conducted using a standard USB microphone and the open source software suite Audacity. The microphone was placed on a table 31 cm from the stimulator head unit. Four 1-s recordings were created with each condition consisting of an initial 250 ms period of silence followed by a single-channel 300 μm 25 Hz sinusoidal vibration lasting 500 ms and ending with another 250 ms period of silence. Audacity provides a contrast analysis tool in compliance with the Web Content Accessibility Guidelines (WCAG 2.0), Success Criteria 1.4.7. This tool was used to calculate the RMS amplitude in decibels (dB) during each vibration and period of silence.

3. Results

This study employed a finger agnosia protocol, in the presence and absence of conditioning stimulation, on healthy subjects in order to demonstrate the capacity of the device for delivering well-controlled vibrotactile stimuli at four independent sites. Additionally, an auditory cue analysis was performed in order to ensure that there were no auditory cues available for the subjects during the finger agnosia protocol. The auditory cue analysis found no indication of any auditory cues being produced by the stimulator during a vibration. The peak amplitude for any channel during a vibration was −42.64 dB (silence is considered to be in the range of −30 dB). The average RMS amplitude (during all vibrations) was −58.90 ± 0.11 dB. The average RMS amplitude during the periods of silence was −58.83 ± 0.10 dB. Comparing each condition's vibration to the immediately preceding silence yielded an average difference in RMS amplitude of 0.05 ± 0.13 dB.

The finger agnosia task was evaluated in order to quantify the ability of subjects to recognize and identify stimulated digits in the absence and in the presence of conditioning stimuli at different amplitudes. This task included seventeen healthy subjects (8 males and 9 females) ranging from 22 to 57 (39.1 ± 2.9) years of age. As shown in Fig. 3, the average percent accuracy in the absence of conditioning stimuli was 98.2 ± 0.9% (n = 17), and accuracy across subjects decreased with increasing amplitude of conditioning stimuli. Conditioning amplitudes of 30 and 40 μm resulted in percent accuracies of 93.7 ± 3.0% and 94.9 ± 4.2%, respectively, and were not statistically significant compared to subject performance in the absence of conditioning stimuli. The effect of conditioning on the finger agnosia task became statistically significant at conditioning amplitudes greater than 50 μm: 89.0 ± 4.2% at 50 μm (p < 0.06) and 60.0 ± 7.6% at 100 μm (p < 0.01). Because the conditioning stimuli at 100 μm resulted in the most significant percentage of incorrect responses compared to the simple finger agnosia protocol, the frequency of inaccurate responses for each digit was quantified (Fig. 4). The results suggested that subjects, on average, made the largest number of inaccurate responses when the correct answer should have been D3 and D4 (percent inaccuracies of 60.0 ± 10.0% and 55.0 ± 14.6%, respectively). Subjects were relatively better at identifying stimulation of D2 (inaccuracy of 15.0 ± 10.0% significantly better than that for D3, p < 0.01) and better at identifying D5, though not statistically significantly more.

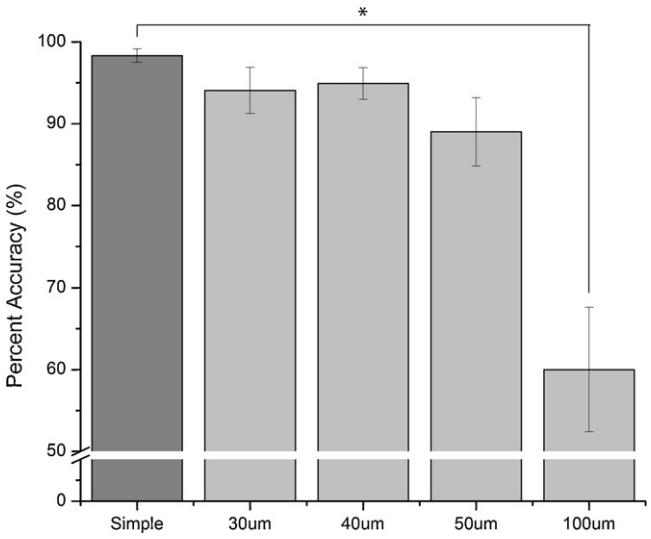

Fig. 3. Average percent accuracy the effect of conditioning stimuli on the finger agnosia task. The average percent accuracy in absence of conditioning stimuli was 98.2 ± 0.9% (n = 17). In the presence of 30, 40, 50, and 100 μm conditioning stimuli, the percent accuracies gradually decreased with increased amplitude of conditioning stimuli: 93.7 ± 3.0% at 30 μm (n = 17), 94.9 ± 4.2% at 40 μm (n = 16), 89.0 ± 4.2% at 50 μm (n = 17, p < 0.06), and 60.0 ± 7.6% at 100 μm (n = 5, p < 0.01).

4. Discussion

The delivery of sinusoidal displacements to a single skin site via mechanical transducer has been used extensively for the study of flutter vibration in both psychophysical and neurophysiological settings for a number of decades. Exemplary uses of such a device are described in Goble and Hollins (1993), Juliano et al. (1989), LaMotte and Mountcastle (1975), Mountcastle et al. (1969), Tannan et al. (2006), Tommerdahl et al. (1993, 1998, 2002), and Vierck and Jones (1970). Typically, stimuli that can be delivered through mechanical transducers – vertical displacement stimulators such as the one originally described by Chubbuck (1966) – were used for studies of somatosensation and are very well equipped to deliver sinusoidal stimuli at a frequency range (1–250 Hz) with amplitudes of sufficient size (between 0 and 1000 μm) to activate a broad range of mechanoreceptors. However, in order to stimulate more than one skin site – either during the course of human psychophysical

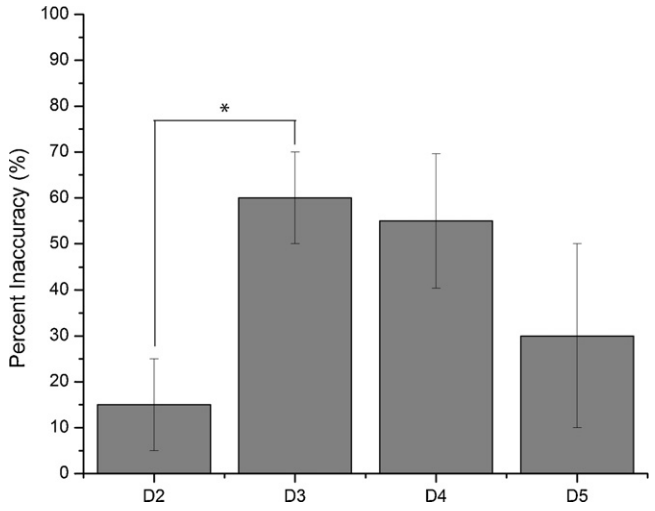

Fig. 4. Average percent inaccuracy on finger agnosia with 100 μm conditioning stimuli. Digits D3 and D4 showed the highest percent inaccuracies of 60.0 ± 10.0% and 55.0 ± 14.6%, respectively. There was a statistically significant observation in accurately recognizing and identifying stimulation of D2 at 15.0 ± 10.0% versus D3 at 30.0 ± 20.0% ($p < 0.01$) and slight discrimination difference between D2 and D4 ($p < 0.08$) in the presence of the 100 μm conditioning stimuli. The other the digit combinations showed no statistical significance in discrimination capability.

testing or animal experimentation – it is necessary to position a second vertical displacement stimulator over the second skin site. Our previous device (described in Tannan et al., 2007a) was designed to address this issue by allowing dual site stimulation with automated two-dimensional probe positioning. Although the device reported by Tannan and colleagues was successfully utilized in a number of studies (Tannan et al., 2005b, 2006, 2007b, 2008; Tommerdahl et al., 2007a,b, 2008), it was cumbersome and not ideal for clinical and clinical research venues. The CM-4, described in this report, has the capacity to quickly and easily adjust to fit to most adult, and many juvenile, hand sizes and can deliver vibrotactile stimuli to the tips of four digits. The ability to simultaneously deliver vibrotactile stimuli to a number of digits allows for a great deal of protocol diversity.

In this report, we described a relatively simple four-site finger agnosia protocol to demonstrate the potential utility of the device. The principle finding in the results of this study is that there is an increase in inaccuracies with increases in the amplitude of concurrent conditioning stimulation delivered during the agnosia task, and the ability to perform the task accurately in the presence of that conditioning stimulation is diminished more in digits D3 and D4 than in digits D2 and D5. The decrease in accuracy with increasing amplitudes of synchronized sinusoidal stimulation is consistent with prior reports of increasing inaccuracies in temporal order judgment (TOJ) in the presence of synchronized and periodic conditioning stimuli. In a study by (Tommerdahl et al. (2007a,b), it was demonstrated that TOJ results obtained from a number of pairs of stimulus sites – unilateral as well as bilateral – were comparable. However, in the presence of a 25 Hz conditioning sinusoidal stimulus which was delivered both before, concurrently and after the TOJ task, there was a significant increase in the TOJ measured when the two stimuli were located unilaterally on digits D2 and D3. In the presence of the same 25 Hz conditioning stimulus, the TOJ obtained when the two stimuli were delivered bilaterally was not impacted. This led to the speculation that the impact that the conditioning stimuli – which only had an impact if they were sinusoidal, periodic and synchronous – had on TOJ measures was due to the synchronization of adjacent cortical ensembles in somatosensory cortex, and that the synchronization of these cortical ensembles could have been responsible for the degradation in temporal order judgment. The conditioning stimuli in this study were also synchronized, periodic and simultaneous, and if the degradation in test performance was due to synchronization of adjacent cortical ensembles similar to what was speculated in the TOJ report, then inaccuracies due to this synchronization would be lower on the digits on the perimeter of the cortical ensemble (i.e., D2 and D5), and the results reflect this prediction. Future studies will consider whether or not subjects with neurological disorders are not impacted by conditioning stimuli, as was found to be the case in subsequent TOJ studies (e.g., TOJ metrics of subjects with autism were not impacted significantly by conditioning stimuli; Tommerdahl et al., 2008).

The degree of inaccuracies in the different digits with increasing conditioning stimulation is also consistent with motor studies of digit interdependencies. In studying the autonomy of finger movements, intended motion in one finger often results in simultaneous movement, or enslavement, of other digits. More specifically, D3 and D4 show the most enslavement, or interdependency, of adjacent digits while D2 is characterized by the greatest independence (Häger-Ross and Schieber, 2000). In observing motor-related cortical potentials (MRCPs), the autonomous nature of D2 was shown to be significantly high while D4 showed the most dependency on other digits (Slobounov et al., 2002). In Fig. 4, D2 demonstrates the lowest inaccuracies in the presence of conditioning stimulation while D3 and D4 exhibit the most; thus, in both the motor and sensory based studies, D2 demonstrates the most independence.

The role of neural communication between adjacent and non-adjacent cortical regions plays an important role in understanding the relationship between neurophysiological mechanisms and sensory percept. The development of new, more versatile devices and methodologies, such as presented in this report, could contribute to bridging decades of neuroscientific research with human perceptual clinical and clinical research studies. One long term goal of our research is to develop sensory based instrumentation and methodologies for the diagnosis and assessment of treatment efficacies for a broad range of neurological disorders, and building this aforementioned bridge could provide new insights into fundamental information processing mechanisms as well as generating perceptual metrics that are more sensitive to alterations in central information processing capacity.

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Somatosensory information processing in the aging population

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While it is well known that skin physiology – and consequently sensitivity to peripheral stimuli – degrades with age, what is less appreciated is that centrally mediated mechanisms allow for maintenance of the same degree of functionality in processing these peripheral inputs and interacting with the external environment. In order to demonstrate this concept, we obtained observations of processing speed, sensitivity (thresholds), discriminative capacity, and adaptation metrics on subjects ranging in age from 18 to 70. The results indicate that although reaction speed and sensory thresholds change with age, discriminative capacity, and adaptation metrics do not. The significance of these findings is that similar metrics of adaptation have been demonstrated to change significantly when the central nervous system (CNS) is compromised. Such compromise has been demonstrated in subject populations with autism, chronic pain, acute NMDA receptor block, concussion, and with tactile–thermal interactions. If the metric of adaptation parallels cortical plasticity, the results of the current study suggest that the CNS in the aging population is still capable of plastic changes, and this cortical plasticity could be the mechanism that compensates for the degradations that are known to naturally occur with age. Thus, these quantitative measures – since they can be obtained efficiently and objectively, and appear to deviate from normative values significantly with systemic cortical alterations – could be useful indicators of cerebral cortical health.

Keywords: aging, sensory, plasticity, adaptation, tactile, somatosensory

INTRODUCTION

There have been a number of significant findings related to both the anatomical and physiological degradation that occurs with normal aging. For example, structural and functional neuroimaging studies have consistently shown evidence of age-related reduction of cerebral cortical volume (Resnick et al., 2003; Raz et al., 2005; Driscoll et al., 2009; Fjell et al., 2009) and changes of white matter integrity in healthy older adults (Gunning-Dixon and Raz, 2000; Bartzokis et al., 2003; Gunning-Dixon et al., 2009). However, a number of researchers have noted that cognitive performance is relatively stable with normal aging (Morse, 1993; Wilson et al., 2002; Van Petten et al., 2004), although some metrics of sensory performance (e.g., thresholds) degrade (Verrillo, 1982; Gescheider et al., 1994; Verrillo et al., 2002; Lin et al., 2005). Dinse made the observation that restoration of function in the aging population is attainable due to the emergence of new processing strategies, and he attributed this to brain plasticity being operational in the aging population (Dinse, 2006). In a recent review, Greenwood put forth a hypothesis that with aging, although there is significant evidence of both anatomical and physiological decline, there is no, or even negative, correlation with cognitive performance. Greenwood largely attributes the undefined compensatory mechanism that allows for maintenance of cortical information processing capacity to cortical plasticity (Greenwood, 2007; Greenwood and Parasuraman, 2010).

Recently, we have developed unique sensory based measures that quantify particular aspects of a subject's central information processing capacity (Tannan et al., 2005a,b, 2006, 2007a,b, 2008; Tommerdahl et al., 2007a,b, 2008; Folger et al., 2008; Francisco et al., 2008; Zhang et al., 2008, 2009, 2011). One particular focus of these studies has been on obtaining measures of centrally mediated adaptation – a process that is a fundamental component of cortical plasticity and operates on multiple time scales (for review, see Kohn, 2007). If cortical plasticity is the mechanism by which cortical information processing capacity is maintained, and if adaptation does, in fact, parallel cortical plasticity, then we would predict that metrics of adaptation would remain constant with normal aging. In terms of adaptation, in this study, we are most concerned with changes that occur in response to short duration (0.2–1 s) repetitive stimulation.

The metrics that we collected across the age spectrum could be broadly defined in one of two categories: those that are peripherally biased and those that are predominantly centrally mediated. We predicted that the measures that are predominantly peripherally mediated would be most sensitive to the impact of aging while measures that are predominantly centrally mediated would be less impacted. The results demonstrate that the peripherally mediated measures, such as threshold detection, were – as previously reported by others – significantly impacted with increasing age. This is not surprising, as most of these measures are primarily related to skin physiology, and it is well established that sensory thresholds do increase with age. Centrally mediated measures, such as those that rely mechanistically on cortical information processing properties such as lateral inhibition and/or adaptation,

however, did not change with age. We viewed this as being consistent with the idea that others (e.g., Dinse, 2006; Greenwood, 2007) have put forth that cortical plasticity is maintained in normal aging and compensates for both anatomical and physiological losses that have been shown to naturally occur with age.

MATERIALS AND METHODS

In this study, 120 healthy subjects from a wide age spectrum (18–70 years) were recruited from the students and employes of the University of North Carolina at Chapel Hill. The subjects were divided into six age groups, 20 subjects in each group. A survey about medication and medical history was filled out by each subject before experimental tests to exclude subjects with a history of neurological impairment. All the subjects were naïve both to the study design and issue under investigation. The study was performed in accordance with Declaration of Helsinki, all subjects gave their written informed consent, and the experimental procedures were reviewed and approved in advance by an institutional review board.

During an experimental session, the subject was seated comfortably in a chair with right arm resting on an arm rest attached to the head unit of a portable four-site vibrotactile stimulator (**Figure 1**; CM4, Cortical Metrics, LLC). Vibrotactile stimulation was conducted via 5 mm diameter probes that come in contact with subject's digit 2 (index finger) and digit 3 (middle finger) of the right hand. The independent probe tips are computer controlled and capable of delivery of a wide range of vibrotactile stimulation of varying frequencies (measured in Hertz) and amplitudes (measured in micrometers). Glabrous pads of digit 2 (D2) and digit 3 (D3) were chosen as the test sites for two reasons: (1) to allow the convenience of access and comfort of the subject, and (2) because of the wealth of neurophysiological information that exists for the corresponding somatotopic regions of cortex in primates. The subject's left hand was holding a two-button response device. During each test, the subject was instructed to press the left/right button when the correct stimulus was perceived on the index/middle finger, respectively.

FIGURE 1 | Photo of the multi-site vibrotacitle stimulator. During an experimental session, subject was seated comfortably in a chair with right arm resting on the arm rest attached to the head unit of the stimulator. Vibrotactile stimulation was conducted via 5 mm probes that come in touch with subject's index and middle finger.

Visual cueing was provided with a computer monitor during the experimental runs. Specifically, an on-screen light panel indicated to the subject when the stimulus was on and when the subject was to respond. An audiometer was used to make sure that no auditory cues were emitted from the stimulator during delivery of the stimuli. Practice trials were performed before each test which allowed the subjects to become familiar with the test, and correct response on five consecutive training trials were required before commencing with each test. The subject was not given performance feedback or knowledge of the results during data acquisition. Stimulus parameters are specified by test algorithms based on specific protocols and subjects' responses during those protocols.

In the current study, a series of metrics were employed to assess each subject's tactile information processing capacity. The total experiment – from start to finish – lasted approximately 30 min and consisted of the following six metrics: (1) simple reaction time (RT); (2) choice RT; (3) static detection threshold; (4) dynamic detection threshold; (5) amplitude discrimination between two concurrent stimuli; (6) amplitude discrimination after pre-exposure to a conditioning stimulus to one of the stimulus sites (single-site adaptation). Exemplary use, technical description, and neurobiological basis of individual metrics have previously been described in detail (Tannan et al., 2007a,b, 2008; Tommerdahl et al., 2007a; Folger et al., 2008; Francisco et al., 2008; Zhang et al., 2009). An overview of the procedures is provided below.

Simple RT was measured for 14 times during an experimental run for each subject. The left panel of **Figure 2A** shows the schematic of the protocol. During each trial a single tap (amplitude in 300 μm) was delivered to D2. The subject was instructed to press a response button as soon as the tap was felt. After subject's response, a delay between 2 and 7 s was placed before the onset of the next trial. For each trial, the RT was recorded as the time interval between stimulation tap and subject's response. In total, 14 simple RTs were obtained for each subject. During the course of data analysis, the two largest and two minimum RT values were excluded in order to eliminate the effects of anticipation and inattention. As a result, a subject's simple RT was calculated as the average of 10 RTs recorded.

Choice RT was measured using a 14-trial two alternative forced choice (2AFC) protocol. The right panel of **Figure 2A** shows the schematic of the protocol. During each trial a single tap (amplitude in 300 μm) was delivered to either D2 or D3; the stimulus location was randomly selected on a trial-by-trial basis in order to minimize subject's inattention and distraction. The subject was instructed to select the skin site (D2 or D3) that received the tap as fast as possible by pressing the left or right button on the response box. The response accuracy was recorded for each trial. After excluding the two largest and two minimum values, the average response time of trials with correct response was considered as a subject's choice RT. The average performance accuracy of all the subjects is 95%.

STATIC DETECTION THRESHOLD

Each subject's vibrotactile detection threshold was measured using a 20-trial 2AFC tracking protocol (for recent description with

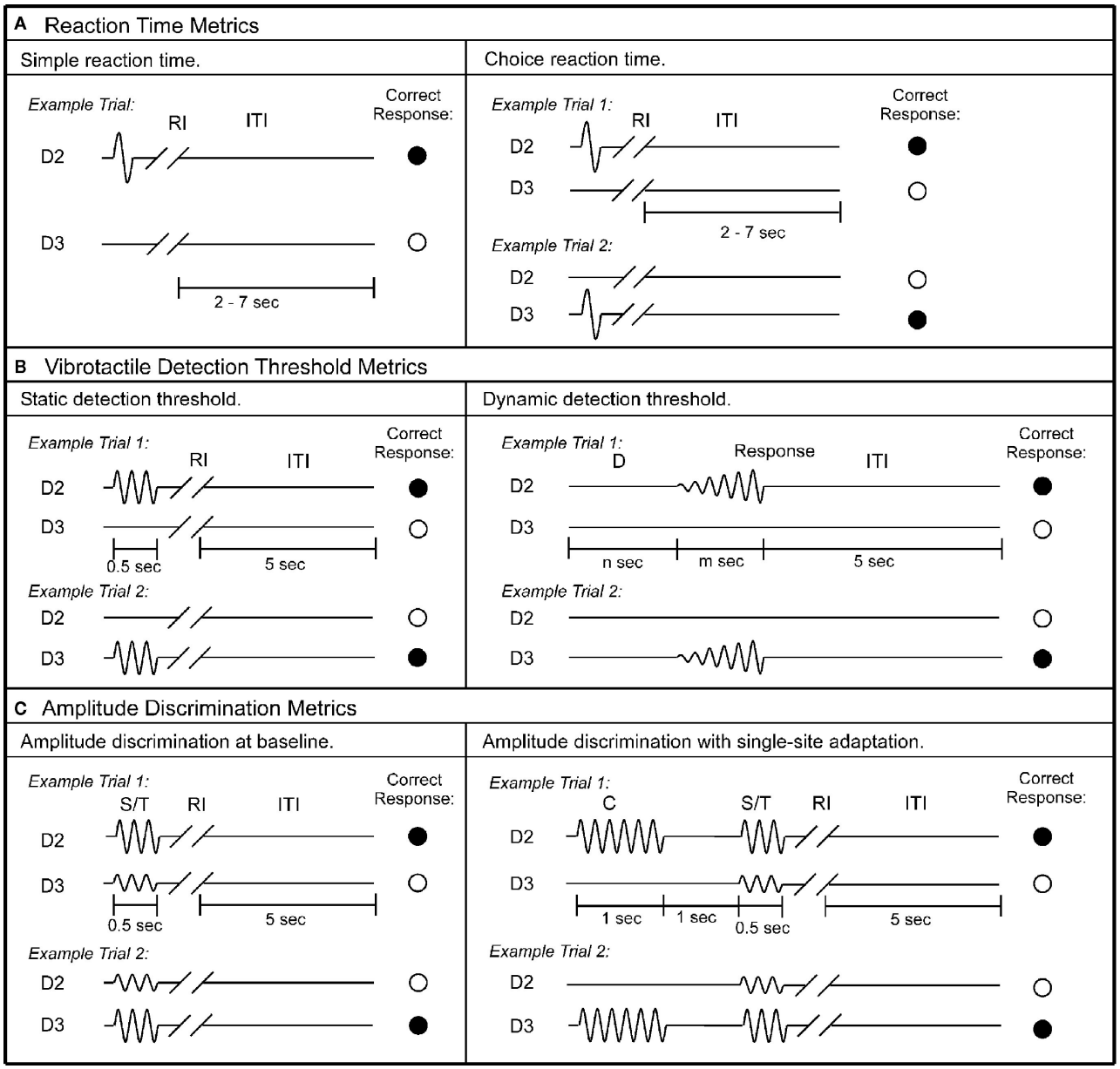

FIGURE 2 | Schematics of the protocols used in this study. (A) Reaction time metrics. Left panel: during each trial of the simple RT task, a single tap was delivered to D2, followed by response interval (RI). Subject was instructed to press a response button as soon as the tap was felt. After subject's response, an inter-trial interval (ITI) between 2 and 7 s was placed before the onset of the next trial. Right panel: during each trial of the choice RT task, a single tap was delivered to either D2 or D3. Subject was instructed to select the skin site that received the tap as fast as possible. **(B)** Vibrotactile detection threshold metrics. Left panel: during each trial of the static detection threshold task, a 25-Hz vibrotactile test stimulus was delivered to either D2 or D3 for 0.5 s. Subject was instructed to select the skin site that perceived the stimulus. A 5-s ITI intervened between subject's response and onset of the next trial. Right panel: during each trial of the dynamic detection threshold task, a delay period (D) (*n* seconds = 0, 1.5, 2, or 3 s) without any stimulation was applied. After the initial delay, a 25-Hz vibrotactile stimulus was delivered to either D2 or D3. The amplitude of the stimulus was initiated from zero and increased in steps of 2 μm/s. The stimulation was terminated with subject response to the perceived stimulus. **(C)** Amplitude discrimination metrics. Left panel: during each trial of the amplitude discrimination task, two 25 Hz vibrotactile stimuli – the standard (S) and test (T) – were delivered simultaneously for 0.5 s. Subject was instructed to choose the stimulus that was perceptually larger. Right panel: the amplitude discrimination task was conducted after single-site adaptation. During each trial, a 25-Hz conditioning stimulus (C) was delivered for 1 s prior to the presentation of the test and standard stimuli.

this experiment setup, see previous studies Zhang et al., 2009). The left panel of **Figure 2B** displays the schematic of the protocol. During each trial a 25-Hz vibrotactile test stimulus (lasts 500 ms) was delivered to either D2 or D3; the stimulus location was randomly selected on a trial-by-trial basis. Following each vibrotactile stimulus, the subject was prompted to select the

skin site (D2 vs. D3) that perceived the stimulation. After a 5-s delay – based on subject response – the stimulation was repeated until the completion of the 20 trials. The stimulus amplitude was started at 15 μm and was modified based on the subject's response in the preceding trial. During the initial 10 trials, a 1-up/1-down algorithm was used for the purposes of amplitude modification. For example, the stimulus amplitude was decreased by 1 μm if the subject's response in the preceding trial was correct. However, it was increased by 1 μm if the response was incorrect. After the initial 10 trials, the amplitude was varied using a 2-up/1-down algorithm (two correct/one incorrect subject response(s) resulted in a decrement/increment, respectively, in the amplitude of the stimulus). The rationale for using 1-up/1-down algorithm in the first 10 trials was to expedite determination of subject's vibrotactile discriminative range without affecting the results, and this approach has been previously reported (Tannan et al., 2006, 2007a,b, 2008; Tommerdahl et al., 2007a,b, 2008; Folger et al., 2008; Francisco et al., 2008; Zhang et al., 2008, 2009, 2011).

DYNAMIC DETECTION THRESHOLD

At the beginning of each trial (as shown in **Figure 2B**, right panel), a delay period (D) which includes no stimulation was applied. Four conditions of delay (*n* seconds) were employed, in separate trials: 0, 1.5, 2, and 3 s. After the initial delay, a 25-Hz vibrotactile stimulus was delivered to either D2 or D3 (the stimulus location was randomly selected on a trial-by-trial basis). The amplitude of the stimulus was initiated from zero and increased in steps of 2 μm/s. The subject was instructed to indicate the skin site that received the stimulus as soon as the vibration was detected. The stimulus amplitude at the time of subject's response was recorded, and only the value with accurate response was used to calculate the subject's average dynamic detection threshold.

AMPLITUDE DISCRIMINATION AT BASELINE

Each subject's amplitude discrimination capacity was assessed using a 2AFC tracking protocol that has been described and implemented in a number of previous studies (Tannan et al., 2007a,b, 2008; Tommerdahl et al., 2007a; Folger et al., 2008; Francisco et al., 2008; Zhang et al., 2008, 2009, 2011). As shown in **Figure 2C** left panel, during the 20-trial experimental run, a vibrotactile test stimulus (T; 25 Hz, amplitude between 105 and 200 μm) was delivered to one digit pad at the same time that a standard stimulus (S; 25 Hz, amplitude fixed at 100 μm) was applied to the other digit pad. The loci of the test and standard stimuli were randomly selected on a trial-by-trial basis. At the beginning of the experimental run, the test amplitude was 200 μm and the standard amplitude was 100 μm. The difference between the amplitudes of the test and standard stimuli was adjusted on the basis of the subject's response in the preceding trial, such that the difference was decreased/increased after a correct/incorrect response, respectively. The step size was held constant at 10 μm throughout the experimental run. The same tracking algorithm as that described for the tactile detection threshold protocol was employed to track the subject's ability to determine the most intense stimulus between the test and standard stimuli [i.e., the subject's difference limen (DL) was determined].

ADAPTATION METRIC

Amplitude discrimination with single-site adaptation. In order to measure the effects that conditioning stimuli have on subsequent test stimuli, the previously described amplitude discrimination protocol was modified such that delivery of the test and standard stimuli was preceded by a single conditioning stimulus to one of the two stimulus sites (as shown in **Figure 2C**, right panel). Specifically, a 25 Hz 200 μm conditioning stimulus (C) was delivered 1 s prior to the presentation of the test and standard stimuli (S/T). The duration of the conditioning stimulus was 1 s, which was followed by a 1-s delay before onset of the simultaneous delivery of the test and standard stimuli. The result of such a protocol modification is that the amplitude discrimination DL is typically significantly elevated after pre-exposure to a single-site conditioning stimulation (Tannan et al., 2007b, 2008; Folger et al., 2008; Zhang et al., 2009, 2011). When the conditioning stimulus is delivered to the same site as the test stimulus, the gain effect of adaptation (reducing the perceived intensity) can be quantified by comparison of the DL obtained in the adapted vs. non-adapted conditions (amplitude discrimination at baseline). The tracking algorithm used in the previously described protocol was employed.

ANALYSIS

One way analysis of variance (ANOVA) and two-sample *t*-test were used to evaluate the difference of the subject's performance across different groups. Data are presented as means and SE. A probability of less than 0.05 was considered statistically significant.

RESULTS

In the current study, a series of sensory perceptual measures was performed on healthy control subjects of different ages (ranging from 18 to 70 years) that assessed: (1) RT; (2) vibrotactile detection threshold; (3) amplitude discrimination capacity; and (4) the impact of adaptation on amplitude discrimination capacity. The results indicate that although RT and sensory thresholds increased as a function of age, the subject's discriminative capacity and the effects of adaptation on performance remained constant across all the age groups tested.

Reaction time increases with age. **Figure 3A** summarizes the group-averaged RT of six age groups. Both choice and simple RTs progressively increase with advancing age. One way ANOVA was performed to compare the mean RT across six age groups, and there is evidence that there are significant differences in the means across groups ($p < 0.001$ for both simple and choice RT). Two-sample *t*-test was employed to compare the mean RT of the subjects under 25 years vs. the mean RT of the subject older than 60 years. There is a significant difference in the mean simple RTs (182 vs. 302 ms) and mean choice RTs (362 vs. 498 ms) with $p < 0.001$. The data suggests an age-related decrement in response speed. Note that for all the age groups, choice RT is always higher than simple RT. The difference between choice RT and simple RT might reflect the duration that it takes for a subject to identify a stimulus location. In **Figure 3B**, the group-averaged RT values are plotted against age. Strong linear relationship (positive correlation) between RTs and age were observed, with $R^2 = 0.99$ for simple RT and $R^2 = 0.95$ for choice RT.

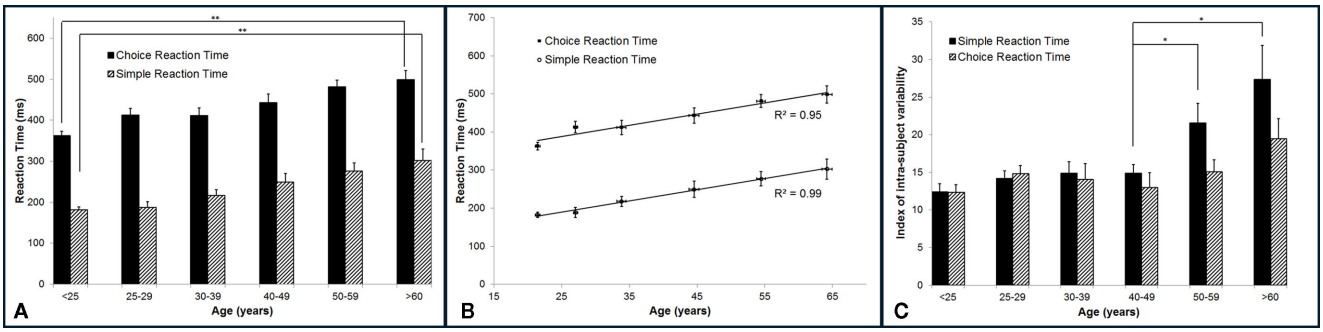

FIGURE 3 | Summary of the group-averaged RTs for six age groups. **(A)** Both simple and choice RT progressively increase with advancing age. Comparing the performance between the subjects under 25 years to the subjects older than 60 years, there is a significant difference in the mean simple RT and choice RT with $p < 0.001$. **(B)** A strong linear relationship (positive correlation) between RTs and age was observed, with $R^2 = 0.99$ for simple RT and $R^2 = 0.95$ for choice RT. **(C)** Summary of the group-averaged index of intra-individual variability for the six age groups. Looking at means of intra-individual variability for simple RT, there is no significant difference in the mean across groups that are younger than 50 years ($p = 0.4$). However, significant difference was found between mean of 40–49 years group and means of 50+ groups ($p < 0.05$). No significant difference was found for choice RT performance across groups ($p = 0.11$).

In the current study, subjects performed each RT test for 14 times. In order to calculate the index of intra-individual variability, the SD of repeated RT measures was normalized to the mean RT for each subject individually. The group-averaged index of intra-individual variability (%) on RT performance was calculated and plotted in **Figure 3C**. One way ANOVA was performed. It was found that there is evidence of significant differences in the means of intra-individual variability for simple RT performance ($p < 0.001$) across six age groups, while no significant differences are found for choice RT performance ($p = 0.11$) across groups. Looking at the intra-individual variability for simple RT by itself, there is no significant differences in the means across age groups younger than 50 years ($p = 0.4$). However, two-sample t-test shows significant difference between mean of 40–49 years age group and mean of 50–59 years age group ($p < 0.05$). The data demonstrates that the group-averaged intra-individual variability remains relatively constant for the subjects younger than 50 years old, while the older subjects (>50 years) have significant higher intra-individual variability.

Vibrotactile detection threshold increases with age. The group-averaged detection thresholds were obtained with two different methods: a static testing paradigm and a dynamic testing paradigm. As shown in **Figure 4A**, the group-averaged static threshold gradually increases with advancing age. Specifically, the averaged static threshold for the subjects who are older than 60 years is 13.95 μm which is about 8 μm larger than that of the subjects under 25 years old (5.42 μm). Since several studies have reported that psychophysical measurement methods had a significant influence on vibrotactile threshold (Maeda and Griffin, 1994; Morioka and Griffin, 2002), the threshold was also measured by a dynamic tracking protocol, in which a continuously increasing stimulus was delivered. Following the same trend as observed with static testing paradigm, the group-averaged dynamic threshold progressively rises with aging. In general, the data suggest an elevated tactile sensitivity for older subjects.

It is noteworthy that all subjects demonstrated a dynamic threshold that was higher than their static threshold. This noticeable difference in the threshold between the two tasks is consistent with previous reports (Morioka and Griffin, 2002; Zhang et al., 2009, 2011). One of the explanations could be linked to the fact that dynamic threshold is RT dependent, while static threshold is independent of RT. If this is simply the case, the difference between dynamic and static threshold should be equal to the product of choice RT and the speed of amplitude increment (2 μm/s) during dynamic threshold measurement. Based on this assumption, we calculated the predicted dynamic thresholds using following equation:

$$\text{Predicted dynamic threshold} = \text{Observed static threshold} + \text{Choice RT} * 2\,\mu\text{m/s}$$

Figure 4B compares the predicted and observed dynamic thresholds, and the predicted values are always significantly smaller than the observed thresholds, strongly suggesting that the difference between the two measures is not simply due to RT. **Figure 4C** is a direct comparison between the two threshold metrics for each age group (actually a ratio of dynamic/static), and it emphasizes not only that the dynamic threshold is always greater than the static threshold, but that this ratio decreases with age. There is a significant difference between the youngest age group and the oldest age group ($p < 0.05$).

Amplitude discrimination capacity and the effects of adaptation were not altered with increases in age. **Figure 5** summarizes the group-averaged amplitude discrimination performance obtained during amplitude discrimination task with or without pre-exposure to a conditioning stimulus (adaptation). The data demonstrate that, in the absence of single-site adaptation, subjects were able to discriminate between a 100 μm and nearly 125 μm stimulus equally well for all the age groups. On the other hand, the delivery of a conditioning stimulus to one of the two stimulus sites prior to the amplitude discrimination task significantly impacted the subject's amplitude discrimination capacity, and the effects of adaptation maintained well across all the age groups. This observed impairment of amplitude discrimination capability

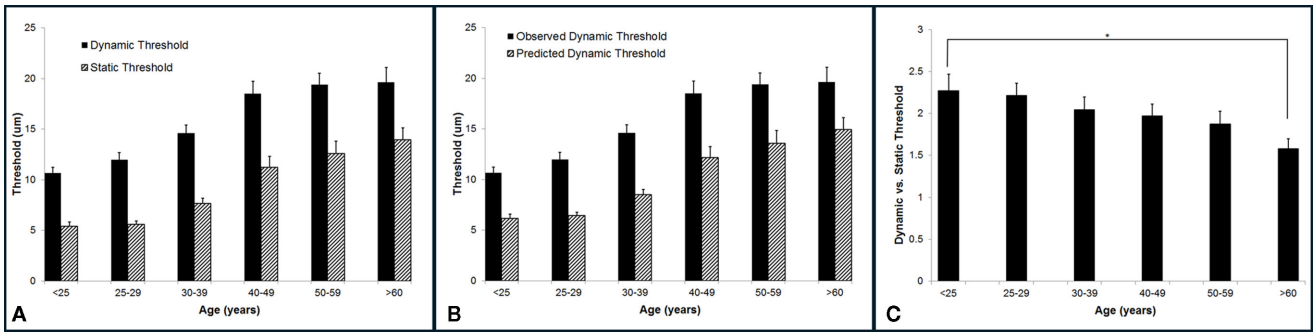

FIGURE 4 | Summary of group-averaged vibrotactile detection thresholds obtained with two different methods across six age groups. (A) Both static and dynamic detection threshold progressively rises with aging. All subjects demonstrated a dynamic threshold that was higher than their static threshold. **(B)** Comparison of the predicted and observed dynamic thresholds. The predicted values are always significantly smaller than the observed thresholds. **(C)** Summary of ratio of dynamic vs. static detection threshold across six age groups. Not only the dynamic threshold is always greater than the static threshold, but the dynamic vs. static ratio decreases with age. There is a significant difference between the youngest age group and the oldest age group ($p < 0.5$).

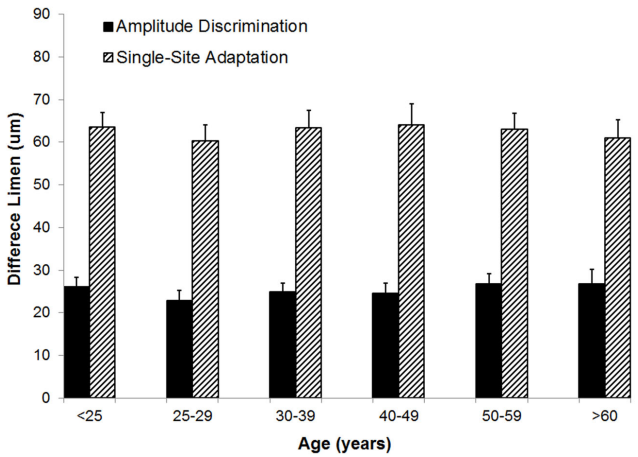

FIGURE 5 | Comparison of difference limen obtained with amplitude discrimination tasks with or without single-site adaptation. There is no significant difference in means across six age groups for both the metric of amplitude discriminative capacity ($p = 0.85$) as well as the adaptation metric ($p = 0.98$).

due to adaptation is consistent with the results of previous studies (Tannan et al., 2007b, 2008; Folger et al., 2008; Zhang et al., 2009). One interpretation of this impairment is that a 1-s conditioning stimulus reduces the perceived intensity of the subsequent test stimulus to the extent that a stimulus with amplitude of approximately 170 μm (compared to 125 μm without adaptation) was perceived as nearly the same in intensity as the 100 μm stimulus. One way ANOVA proves that there is no difference in means across six age groups for the amplitude discrimination task with adaptation ($p = 0.98$) or without adaptation ($p = 0.85$). To summarize the finding across the age spectrum, there is no significant difference in amplitude discrimination performance between subjects of different age groups indiscriminative capacity with or without the presence of single-site conditioning stimuli. In other words, both the metric of amplitude discriminative capacity as well as the adaptation metric (the degree to which amplitude discriminative capacity changed with the conditioning stimulus) were maintained with increases in age.

DISCUSSION

The present study evaluated the tactile information processing capacity of healthy human subjects across a wide age range (18–70 years). Six tests were performed to assess: (1) simple and choice RT; (2) vibrotactile detection thresholds; (3) amplitude discrimination capacity; (4) the effects of adaptation on amplitude discrimination capacity. While the results of peripherally mediated measures demonstrated significant increases in RT and detection threshold with age, the subjects' performance on the centrally mediated measures did not change. Specifically, the amplitude discrimination capacity and the impact of adaptation on performance were maintained with age. If adaptation is a metric that parallels cortical plasticity, the results of the current study suggest that the central nervous system (CNS) in the aging population is still capable of plastic changes, and this cortical plasticity could be the mechanism that compensates for the degradations that are known to naturally occur with age.

Among many cognitive skills, speed of information processing is considered to be especially prone to aging effects. Prior studies have shown a significant increase in RT between 20 and 60 year olds (Fozard et al., 1994; Ratcliff et al., 2001), and this compares favorably with the results obtained in this study. In the current study, the subject's tactile information processing speed was assessed with two well established tasks: simple RT and choice RT tasks. We found that group-averaged RT was positively correlated with the average age for each group, with a correlation coefficient of 0.99 for simple RT and 0.95 for choice RT. Several studies have speculated the reasons for slowing RT with age, and factors other than simple speed of nerve transmission are most often cited. For example, human white matter integrity has been found to significantly correlate with information processing speed (Deary et al., 2006; Madden et al., 2009; Vernooij et al., 2009; Penke et al., 2010). Vernooij et al. (2009) conducted diffusion tensor imaging (DTI) scans and cognitive tasks in a sample of 860 older adults 61–92 years of

age. It has been found that performance on tests that rely on processing speed degrades significantly with declining white matter integrity of the whole brain. Since many of these studies were performed on older healthy subjects without signs of mild cognitive impairment or dementia, the increase of RT might simply represent the effects of normal aging on basic cognitive function. In the context of the current study, we speculate that the increased mean RT could be the result of both decreased nerve transmission speed with age as well as the age-related decline in white matter integrity.

Increases in intra-individual variability on RT performance have been observed for older subjects compared with younger subjects. For example, it has been shown that inconsistency across trials on RT performance increases with age (Hultsch et al., 2000, 2002; Gorus et al., 2008; Bunce et al., 2010). In this report, we found that while the group-averaged intra-individual variability remains relatively constant for the subjects younger than 50 years old, the older subjects (>50 years) have significant higher intra-individual variability. In other words, older subjects showed greater inconsistency than younger subjects in response speed. Several studies have demonstrated that performance variability has the potential to be a good indicator of neurological disturbance and may be a good marker of preclinical status of dementia. For example, Bunce et al. (2010) found greater frontal white matter lesions were associated with higher intra-individual variability in choice RT in middle-aged healthy adults. Hultsch et al. (2000) also demonstrated that performance variability was greater in patients with mild dementia than in healthy elderly subjects. As a result, measures of intra-individual variability may be a plausible behavioral indicator of aging-induced central neurological disturbances and may be able to serve as a valuable early marker of neurodegenerative disease.

Tactile detection threshold (a measure which determines the minimum stimulus intensity that can be perceived), has been documented to increase (due to decreased sensitivity) with age (Verrillo, 1977, 1979, 1980; Thornbury and Mistretta, 1981; Kenshalo, 1986; Gescheider et al., 1994; Lin et al., 2005). In the current study, the data is consistent with prior observations and shows degraded vibrotactile sensitivity (at 25 Hz) with increasing age. In order to determine if mechanisms involved in processing sub-threshold vs. threshold stimuli could be differentiated, tactile detection thresholds were collected using two different protocols. "Static" threshold is the minimum constant-amplitude stimulus detected, and "dynamic" threshold refers to the detection threshold measured with a stimulus that is increased from zero intensity to a detectable level (Zhang et al., 2009, 2011). It is noteworthy that all subjects demonstrated a dynamic threshold that was higher than their static threshold. This noticeable difference in the threshold between the two tasks is consistent with previous reports (Morioka and Griffin, 2002; Zhang et al., 2009, 2011). Since an argument could be made that the primary difference between the two measures is one of RT – dynamic threshold is RT dependent, while static threshold is independent of RT – we directly compared the actual results vs. results predicted based on this RT difference. As demonstrated in **Figure 4B** of Results, the difference between the observations obtained by the two methods could not be explained by RT alone. An alternative possibility – and one that the authors have recently proposed (Tommerdahl et al., 2010; Favorov and Kursun, 2011; Zhang et al., 2011) – is that the difference between the two threshold metrics is impacted significantly by feed-forward inhibition that is generated by the initial sub-threshold stimulus that occurs when the dynamic threshold test is ramped from a null to a detectable level. Thus, the sub-threshold stimulus delivered by the dynamic threshold test actually leads to the initial inhibition, or adaptation, that ultimately requires a larger stimulus to reach detectable levels.

One of the interesting findings of the current study is that although the subjects' vibrotactile detection threshold went up with age, their amplitude discrimination capacity was maintained. Specifically, subjects in all age groups demonstrated a similar ability to differentiate two supra-threshold stimuli that are delivered simultaneously to the skin. It should be noted that this amplitude discrimination task was conducted at supra-threshold levels (approximately 10× normative thresholds), and all subjects had approximately the same amplitude discriminative capacity at the amplitudes used. Thus, while the decline of tactile sensitivity is considered to be influenced predominantly by peripheral factors, we speculate that the ability to discriminate between two supra-threshold stimuli is more influenced by centrally mediated factors and would be only moderately influenced by changes in the periphery. This hypothesis was derived, in part, from studies which demonstrated that localized increases in the magnitude of the SI cortical response (Simons et al., 2005, 2007; Friedman et al., 2008) paralleled the changes in the ability of human subjects to distinguish between different intensities of skin stimulation (i.e., amplitude discrimination; Francisco et al., 2008).

To investigate potential changes in cortical plasticity with normal aging, the effect of single-site adaptation on amplitude discrimination capacity was measured. Previous studies using this adaptation metric demonstrated that a conditioning stimulus delivered to one of the two sites before the amplitude discrimination task significantly altered a subject's ability to determine the actual difference between the two stimuli (Tannan et al., 2007b, 2008) by introducing a confound. In other words, the conditioning stimulus makes the subsequent stimulus, at the conditioned site, feel weaker and consequently, amplitude discriminative capacity is reduced. Neurophysiological studies have demonstrated that the effects of reduced intensity due to adapting stimulation are possibly attributable to a reduction in the responsivity of central neurons after prolonged or repetitive stimulation (Lee and Whitsel, 1992; Lee et al., 1992). When the single-site adaptation measure is examined across a number of subject populations with compromised CNS – as may be the case with a neurodevelopmental disorder: autism (Tannan et al., 2008), acute pharmacological block (Folger et al., 2008), or a chronic pain condition (Zhang et al., 2011) – the adaptation metric is significantly diminished from that of the control population. These findings suggest that the method could be viewed as a potential indicator or marker of systemic cortical alterations, as adaptation, at this short duration time scale, is impacted by a number of factors (for discussion, see Tannan et al., 2007b, 2008; Tommerdahl et al., 2007a, 2010; Folger et al., 2008; Francisco et al., 2008; Zhang et al., 2009, 2011).

Evidence from a wide range of studies has demonstrated that while there are aspects of anatomical and functional degradation with age, the CNS is still capable of plastic changes. For instance, in a series of studies, Dinse and colleagues reported

that experimental or environmental stimulations could induce use-dependent plasticity in older animal as well as human subjects at both cortical and behavioral level (Hilbig et al., 2002; Li and Dinse, 2002; Dinse, 2005, 2006; Dinse et al., 2006; Kalisch et al., 2008, 2009; Kattenstroth et al., 2010). Specifically, it has been found that aged rats exposed to an enriched environment showed complete recovery from the age-related enlargement of RFs of the hindpaw in somatosensory cortex typically found in animals housed in standard conditions (Hilbig et al., 2002). At the behavioral level, repetitive sensory stimulation procedures resulted in improvement of tactile acuity in elderly individuals, a phenomenon based on synaptic plasticity (Dinse, 2005; Dinse et al., 2006). In this study, we found that the effects of adaptation remain relatively constant across healthy populations regardless of age. Since adaptation is an important feature of cortical information processing that apparently remains intact with normal aging, it could be an important feature to assess in the aging population. Deviations from normative values could be an early indicator of neurodegenerative disease; studies directly addressing this issue are currently ongoing and will be reported in the near future.

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